REMARKS

Amendments to the Specification

Applicants have amended the first paragraph of the specification to delete the claim to priority to the Czechoslovakian patent application PV-709-92 (filed March 11, 1992). The reason for that amendment is explained below under the subheading "Claim to Priority. . . ."

Amendments to the Claims

Independent Claims 22, 30 and 42 have been amended to point out with more particularity and clarity the subject matter regarded by the Applicants as their invention. The independent claims have been amended to specify that the claimed anti-idiotype antibody "comprises an internal image **corresponding to said epitope**" of said MN protein or of said MN polypeptide, "wherein said MN protein is encoded by a nucleic acid selected from the group consisting of (a) SEQ ID NO: 1; and (b) polynucleotides that differ from SEQ ID NO: 1 due to the degeneracy of the genetic code . . . " [claim 22 as amended], or

> wherein said MN polypeptide is encoded by a nucleic acid that comprises a polynucleotide containing at least 25 nucleotides, said nucleic acid being selected from the group consisting of:
>
> (a) SEQ ID NO: 1; and

(b) polynucleotides that differ from SEQ ID NO NO: 1 due to the degeneracy of the genetic code.

[Claim 42 as amended.]

The phrase "**corresponds to an epitope of an MN protein/polypeptide**" has been defined in the Specification, and has been added to the independent claims to specify that the anti-idiotype antibodies comprise functional mimics of MN protein epitopes, that confer protective immunity and/or anti-tumorigenic activity when administered as a vaccine.

> **The term "corresponding to an epitope of an MN protein/polypeptide"** will be understood to include the practical possibility that, in some instances, **amino acid sequence variations of a naturally occurring protein or polypeptide may be antigenic and confer protective immunity against neoplastic disease and/or anti-tumorigenic effects**. Possible sequence variations include, without limitation, amino acid substitutions, extensions, deletions, truncations, interpolations and combinations thereof. **Such variations fall within the contemplated scope of the invention provided the protein or polypeptide containing them is immunogenic and antibodies elicited by such a polypeptide or protein cross-react with naturally occurring MN proteins and polypeptides to a sufficient extent to provide protective immunity and/or anti-tumorigenic activity when administered as a vaccine**.

[Instant specification, page 82, lines 11-21; emphasis added.]

The Specification clearly indicates that the claimed anti-idiotype antibodies are functional mimics of MN proteins/polypeptides. For example at page 13, lines 12-17, the instant Specification states:

> Disclosed herein are biologically active MN proteins and MN polypeptides that are useful as vaccines to protect vertebrates, preferably mammals, more preferably humans, against neoplastic diseases associated with abnormal MN expression. Such vaccines are also useful to boost a patient's immunity to such a disease. **Such vaccines can alternatively comprise an anti-idiotype MN-specific antibody.**

[Emphasis added.] Another such example can be found in the Specification at page 75, lines 20-25 which reads:

> Uemura et al., Biotherapy (Japan) 10(3): 241-244 (1996) (English summary) define an **anti-idiotype antibody (Ab2)** as "an antibody directed against an antigenic determinant located within a variable region of the immunoglobulin molecule. **Ab2 mimicking the normal antigen (so-called internal image Ab2) may be used as a surrogate antigen for vaccination to trigger the host's immune system** specifically against the nominal antigen."

[Emphasis added.]

The independent claims 22, 30 and 42 have been further amended for particularity and clarity by eliminating original subclaim (b), as well as the phrase in original subclaim (c) that refers to original subclaim (b). Those subclaim amendments

were made to point out with more particularity and clarity the subject matter regarded by the Applicants as their invention in view of the above-discussed amendment to each of the independent claims, which amendment adds the phrase "wherein said anti-idiotype antibody comprises an internal image corresponding to said epitope of said MN protein. . . " or ". . . to said MN polypeptide. . . ."

Independent claims 30 and 42 have been further amended for particularity and clarity to point out that "said epitope of said MN polypeptide is an epitope found in the MN protein encoded by SEQ ID NO: 1." SEQ ID NO: 1 is the full-length MN cDNA (1522 bps) that encodes native MN protein as shown in Figure 1. That MN cDNA is discussed in the instant Specification at least at page 7, lines 12-23, at page 10, lines 15-24, and at page 23, lines 27-29.

New Claims 53, 54 and 55

New claims 53, 54 and 55 have been added to point out with more particularity and clarity the subject matter regarded by the Applicants as their invention. New Claims 53, 54 and 55 depend on independent Claims 22, 30 and 42, respectively. Each of the new claims point out that "the second antibody [which]

specifically binds to an MN protein epitope" can be "a biologically active antibody fragment."

Support for new Claims 53, 54 and 55 can be found at least at page 68, lines 18-20 of the instant Specification, which reads:

> The term "antibodies" is defined herein to include not only whole antibodies but also biologically active fragments of antibodies, preferably fragments containing the antigen binding regions.

Applicants respectfully submit that the addition of new Claims 53, 54 and 55 does not add any new matter.

Conclusion about Amendments

Applicants respectfully conclude that no new matter has been entered by the above amendments and the addition of new Claims 53, 54 and 55. Claims 22-23, 30-31, 36-38, 42-43, 46-48 and new Claims 53, 54 and 55 are now pending and under examination. Applicants respectfully request entry of the above amendments and reconsideration and allowance of the claims as amended.

New Grounds of Rejection (Sections 4 and 15 of Final Office Action)

The Examiner indicates at page 2 (section 4) and at page 16 (section 5) that the Final Office Action contains new grounds of rejection. Applicants respectfully request clarification and identification of the new grounds of rejection.

Telephone Interview of March 7, 2005

Applicants gratefully acknowledge the telephone interview granted by Examiners Larry Helms and David Blanchard on March 7, 2005. In that interview, Applicants proposed an amendment to the independent claims to address the 35 USC 112, 1st paragraph rejection. The proposed amendment specifies that the claimed anti-idiotype antibody comprises an internal image that corresponds to an MN protein/polypeptide "epitope," wherein said MN protein/polypeptide is encoded by SEQ ID NO: 1 or by polynucleotides that differ from SEQ ID NO: 1 due to the degeneracy of the genetic code. The Examiners indicated that such an amendment would be acceptable.

Further, Applicants respectfully requested clarification of the nature of the two §103(a) rejections in view of the sentence in the Office Action at the bottom of page

11 reading that "Applicant's arguments are not persuasive in the absence of objective evidence providing a factual basis that **the monoclonal antibody M75 was not publicly available.**" [Emphasis added.] Applicants questioned whether that sentence meant that the 103(a) rejections were being based on a "public use" in the United States more than a year prior to the priority date for the subject application under 35 U.S.C. §102(b), which rejection Applicants respectfully pointed out was a different and new rejection than that based upon the "printed publication in this or a foreign country . . . " part of 35 U.S.C. §102(b). Examiner Helms indicated that a 103(a)/102(b) "public use" rejection was not what had been intended, but that "publicly available" was used in the sense that he had assumed that the Oosterwijk et al., WO 88/08854 application had been accompanied by a deposit [in an international depository] of the hybridoma producing the G250 monoclonal antibody ("Mab").

Applicants responded that in fact no such deposit of the G250 hybridoma had been made in conjunction with WO 88/08854. Applicants pointed out that the G250 hybridoma was not deposited at an International Depository under the Budapest Treaty until September 11, 2001 as recorded in Example 1 of US 2004/0077081 A1 at page 3 (col. 1), where Oosterwijk et al. admitted that although "a general immunization protocol" was

given in WO 88/08854, that in WO 88/08854 "[f]urther informations, e.g., a molecular characterization of the G250 antibody and the G250 hybridoma cell are lacking."

Applicants also pointed out that none of the prior art references, notably neither Pastorekova et al. nor Oosterwijk et al., identified or characterized the MN protein or any MN nucleic acid. The MN amino acid sequence and MN cDNA sequence were first disclosed in the earliest U.S. priority application for the instant application, filed Oct. 21, 1992.

Applicants further informed the Examiners that Wilex, the company working with Oosterwijk et al. on the G250 Mab had unsuccessfully opposed the Zavada et al. granted European patent, corresponding to the earliest U.S. priority application to the instant application, and then taken a license under the Zavada et al. patents/applications. *Examiner Helms indicated that such evidence was persuasive evidence of nonobviousness,* and that Applicants should enter the above information into the record in the response to the Final Office Action.

35 U.S.C. Section 112, First Paragraph Rejection (Section 10 of Final Office Action)

Applicants respectfully acknowledge with gratitude and agreement the Advisory Action's statements under the

continuation of 5 that if Applicants' response of April 11, 2005 were entered that it would "overcome . . . the rejection of claims 22 and 46 under 35 U.S. C. 112, first paragraph, for lack of enablement."

Applicants have amended the independent Claims 22, 30 and 42 to indicate that the claimed anti-idiotype antibody "comprises an internal image corresponding to said epitope" of an said MN protein or said MN polypeptide, "wherein said MN protein is encoded by a nucleic acid selected from the group consisting of (a) SEQ ID NO: 1; and (b) polynucleotides that differ from SEQ ID NO: 1 due to the degeneracy of the genetic code . . . " [claim 22 as amended], or

> wherein said MN polypeptide is encoded by a nucleic acid that comprises a polynucleotide containing at least 25 nucleotides, said nucleic acid being selected from the group consisting of:
>
> (a) SEQ ID NO: 1; and
>
> (b) polynucleotides that differ from SEQ ID NO NO: 1 due to the degeneracy of the genetic code.

[Claim 42 as amended.]

As indicated above under the REMARKS, the phrase "corresponding to an epitope" of an MN protein or an MN polypeptide has a specific meaning as defined by the instant Specification, to mean that the anti-idiotype antibody comprises an immunogenic functional mimic of an MN protein epitope. The

phrase "comprises an internal image corresponding to said epitope of said MN protein/polypeptide" then means that the claimed anti-idiotype antibody is immunogenic, and that antibodies elicited by the claimed anti-idiotype antibody "**cross-react with naturally occurring MN proteins and polypeptides to a sufficient extent to provide protective immunity and/or anti-tumorigenic activity when administered as a vaccine**." [Instant Specification, page 82, lines 19-21; emphasis added.]

As indicated above under the REMARKS, the Specification clearly indicates that the anti-idiotype antibodies of Applicants' invention are functional mimics of MN proteins/polypeptides. The independent claims, as amended, set forth that attribute of functional mimicry with particularity and clarity and address the Examiner's concern that the previous wording of the independent claims could encompass "anti-idiotypic antibodies [that] would not express three-dimensional shapes that resemble the structure of the natural MN antigen." [Final Office Action, page 4.] As amended, Claims 22, 30 and 42 clearly refer only to anti-idiotype antibodies that mimic the linear or conformational epitopes of the native MN protein/polypeptides.

Response to Advisory Action Concerning New Matter and 112, 1st Paragraph Rejection Applied to Claims 30 and 42

However, the Advisory Action, while finding that the 112, 1st paragraph rejection was overcome by the Applicants' April 11, 2005 response as to claims 22 and 46, found

> [t]the amendments to claims 30 and 42 raise the issue of new matter. . . . The disclosure of specific monoclonal antibodies that bind to the MN protein and the identification of the epitopes that are recognized by these antibodies does not provide adequate written support for the broader claimed subject matter, i.e., anti-idotypic antibodies that bind to any antibody that binds to just any fragment of the MN protein that is at least 8 amino acids in length.

Applicants respectfully submit that the above additional amendments for particularity and clarity to claims 30 and 42 address the new matter issue and what remains of the subject 112, first paragraph, lack of enablement rejection.

Claims 30 and 42 have each been amended for particularity and clarity to point out that the "epitope of said MN polypeptide is an epitope found in the MN protein encoded by SEQ ID NO: 1. . . ." As pointed out above, SEQ ID NO: 1 is the full-length MN cDNA that encodes the native MN protein shown in Figure 1. Applicants respectfully, but emphatically submit that the additional amendments to independent claims 30 and 42

point out with abundant particularity and clarity, [as is true for the other independent claim 22 (from which the Examiners have lifted the subject rejection)], that the claims are to anti-idiotype antibodies to idiotypes that specifically bind to epitopes that are found on naturally occurring MN protein.

Applicants respectfully conclude that the above amendments to the independent claims 30 and 42 meet and overcome the new matter rejection and the remaining part of the rejection under 112, first paragraph. Applicants respectfully remind the Examiner that the Advisory Action under the continuation of 5 indicates that if entered, "the applicant's [April 11, 2005] response would overcome the rejection of claims 22 and 46 under 35 U.S.C. 112, first paragraph. . . ." Applicants respectfully request that the Examiner reconsider and withdraw this rejection as to all pending claims in view of the above amendments and remarks.

Claim to Priority (Page 10 of Office Action)

The Office Action states at page 10 that the

> Czechoslovakian Patent application PV-709-92 discloses the M75 monoclonal antibody secreted from the hybridoma VU-M75. This does not provide adequate descriptive support for the instantly claimed invention, which is drawn to anti-idiotypic antibodies that mimic the MN protein.

Applicants respectfully point out that those statements are consistent with the Applicants' position that without possession of the M75 monoclonal antibody or another MN-specific antibody, and/or the MN amino acid or cDNA sequence, one of skill in the art would not be able to make reproducibly a MN-specific antibody, and would have no idea how to make the claimed anti-idiotype antibodies comprising an internal image corresponding to an MN protein/polypeptide epitope.

Applicants respectfully point out that analogously none of the prior art references cited in the Office Action, notably neither Pastorekova et al. nor Oosterwijk et al. (WO 88/08854) nor Oosterwijk et al. (1986), disclose how to produce an MN-specific antibody reproducibly, let alone the claimed anti-idiotype antibodies, nor do such prior art references characterize or provide the MN amino acid sequence or MN cDNA sequence. The Czechoslovakian patent application PV-709-92 basically discloses at least as much information about the M75 Mab as does Pastorekova et al.

Applicants respectfully withdraw priority from the Czechoslovakian patent application PV-709-92, as indicated above in the amendment to the instant specification.

35 U.S.C. Section 103 Rejections (Sections 11-13 of Office Action)

Applicants gratefully again acknowledge the March 7, 2005 telephone interview with Examiners Larry Helms and David Blanchard. Applicants respectfully also again point out that the phrase "publicly available" as used in the Final Office Action was discussed in that telephone interview, and that the Examiners informed the Applicants that that phrase was not equivalent to that of "public use" in 35 U.S.C. §102(b), but was used in that the Examiners had assumed that the hybridioma which secretes the G250 Mab had been deposited in an international depository at the time of the publication of the cited prior art references. Applicants appreciated the Examiners' attention to and consideration of Applicants' information provided during the interview, regarding the lack of such a deposit of the G250 hybridoma, the lack of enablement to produce the G250 Mab or any MN-specific antibody reproducibly, and the absence of any information or characterization concerning the MN protein or MN cDNA at the earliest U.S. priority date claimed for the instant application, that is, October 21, 1992.

103(a) Rejection over Pastorekova et al. Withdrawn

Applicants acknowledge with gratitude and agreement the Advisory Action's withdrawal (in the continuation of 5) of the rejection of claims 22-23, 30-31, 36-38 and 46-48 under 35 USC 103(a) as being unpatentable over Pastorek et al. in view of Raychaudhuri et al. Applicants therefore are not including the section from the April 11, 2005 response that addresses that rejection. If it is advisable for the Applicants to do so, Applicants would gladly submit that section of the April 11, 2005 response either by incorporation by reference or in a Supplemental Response.

Response to the Advisory Action's Comments on Maintaining the 35 USC 103(a) Rejections Based upon the Oosterwijk et al. (a) and (b) References

The Advisory Action under the "Continuation of 11" reminds the Applicants that

> the rejected claims are not drawn to any particular antibody, or even the G250 monoclonal antibody. Further, applicant has not provided any evidence or arguments why one of ordinary skill in the art following the teachings of Oosterwijk [a] and using renal cell carcinomas as a source of antigen would not produce antibodies that recognize the MN protein expressed by renal cell carcinomas.

> With respect to the rejection of claims 22, 30, 36-38, 42-43 and 46-48 udner [sic] 35 U.S.C. 103(a) as being unpatentable over Oosterwijk et al [b] as evidenced by Uemure [sic] et al and Pastorek et al in view of Raychaudhuri et al, applicant argues that the G250 antibody or hybridoma producing the antibody and not been deposited and one of skill in the art would not have been able to produce the G250 monoclonal antibody reproducibly. Further, applicant argues that the G250 protein or nucleic acid been characterized or identified as of the earliest effective filing date of the instant application, i.e., October 21, 1992. In response, applicant is reminded that the rejected claims are not drawn to any particular antibody, or even the G250 monoclonal antibody. Further, applicant has not provided any evidence or arguments why one of ordinary skill in the art following the teachings of Oosterwijk [b] and using renal cell carcinomas as a source of antigen would not produce antibodies that recognize the MN protein expressed by renal cell carcinomas.

Applicants respectfully but most forcefully argue that until the disclosure of their October 21, 1992 U.S. application including their Budapest Treaty deposit at the ATCC of the VU-M75 hybridoma, that secretes the MN-specific M75 monoclonal antibody, no one of skill in the art would have had any way of recognizing whether or not they had an anti-idiotype antibody to an idiotype of a second antibody which specifically binds to an **MN protein epitope**, and most certainly would not have been so

instructed by either of the Oosterwijk et al. references which taught away from the characteristics of the **MN protein**.

As indicated in the relevant portions of the April 11, 2005 response and earlier responses (on which the Applicants rely), one of skill in the art would need to have the MN protein, which long after the priority date for the instant invention was found to be the same as the G250 protein. However, the Oosterwijk et al. (a) and (b) references instead of providing any identifying characteristics of the MN/G250 protein, which protein Oosterwijk et al. had not been able to isolate until long after the priority date for the instant claims, taught away from any one of skill in the art from recognizing the MN protein that would later be discovered by Zavada et al.

Applicants respectfully point out that the anti-idiotype antibodies of the subject claims are functional mimics of the epitopes of naturally occurring MN protein. How could one of skill in the art possibly know prior to the disclosure by Zavada et al., who discovered the MN protein and gene, whether they had an anti-idiotype antibody to an idiotype of a second antibody that specifically binds to an MN protein epitope with no knowledge of the MN protein? Whether said second antibody is the G250 Mab or any other antibody prepared according to the

methods of the Oosterwijk et al. (a) and (b) references, one of skill in the art would have no idea if said second antibody specifically bound to a yet undiscovered MN protein, and from which, as explained in the April 11, 2005 response and earlier responses, the Oosterwijk et al. (a) and (b) cited references taught away.

There is nothing in the art prior to the priority date of the instant application that would suggest to one of skill in the art how to prepare MN-specific antibodies reproducibly by any procedure, *a fortiori*, how to prepare anti-idiotype antibodies to idiotypes of said MN-specific antibodies, which idiotypes specifically bind to epitopes of naturally occurring MN protein. How would one of skill in the art be able to screen for MN-specific antibodies without any knowledge of the MN protein? *A fortiori*, how would one of skill in the art screen for such MN-specific antibodies based on the Oosterwijk et al. (a) and (b) references which teach away from the characteristics of the MN protein?

The Federal Circuit clearly pointed out in In re Robertson, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999):

> If the prior art reference does not expressly set forth a particular element of the claim, that reference still may anticipate if that element is "inherent" in its disclosure. To establish inherency, the

> extrinsic evidence "must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill." . . . **"Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result form a given set of circumstances is not sufficient."**

[Emphasis added.]

The Oosterwijk et al. (a) and (b) references as pointed out below and in Applicants' April 11, 2005 response and earlier responses, only used "a cell homogenate from primary RCC [renal cell carcinoma] lesions obtained from different patients" and thus "an unspecific material . . . as an immunogen." [Oosterwijk et al.'s later PCT application, WO 02/062972, page 2, lines 9-11.] **At any one time, perhaps about 100,000 proteins are being expressed in a cell, and thousands of proteins are being expressed on the surface of a cell.** Therefore, there were **sure to be a great number of antigens in the cell homogenate used for immunization** in the process of the Oosterwijk et al. (a) and (b) references. **It would be obvious to one of skill in the art that the Oosterwijk et al. method of producing hybridomas and screening** antibodies by selecting those that react to renal cell carcinoma (RCC) but not to normal kidney tissue, **would produce a very large spectrum of different**

antibody secreting hybridomas. Would any of those be MN-specific? One can only guess.

Would an antibody selected from that large spectrum of antibodies produced by the procedure of the Oosterwijk et al. (a) and (b) references be MN-specific? How would one of ordinary skill in the art know before Zavada et al.'s discovery of the MN protein? Again the Federal Circuit clearly states in In re Robertson, supra: **"'Inherency . . . may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.'"**

What did the Oosterwijk et al. (a) and (b) references teach one of skill in the art about the MN protein, let alone MN-specific antibodies, and further let alone anti-idiotype antibodies that bind to idiotypes of MN-specific antibodies, when Oosterwijk et al. provide no biochemical characterization about the G250 antigen, and were not sure if the G250 antigen was even a protein.

The U.S. Supreme Court in 1881 in Tilghman v. Proctor, 102 U.S. 707 (1881) held that an accidental, unintended and unappreciated production of a subject product or process does not constitute anticipation. The Federal Circuit in In re Spada, 15 USPQ2d 1955, 1657 (Fed. Cir. 1996) held that in order

to anticipate, **"the [prior art] reference must describe the applicant's claimed invention sufficiently to have placed a person of ordinary skill in the field of the invention in possession of it."** The Oosterwijk et al. (a) and (b) references do not come anywhere close to putting one of skill in the art in possession of the claimed invention, and there is no prior art available that would enlighten one of skill in the art how to overcome Oosterwijk et al.'s teaching away from the instantly claimed invention.

One can not use hindsight from Zavada et al.'s discovery to change the disclosure of the Oosterwijk et al. (a) and (b) references to suggest how one would make and use the claimed invention. Applicants respectfully point out the extremely well-established legal principle that **the use of hindsight is impermissible to establish obviousness.**

Applicant respectfully argues that a prima facie case of obviousness has not been established against the claims of the invention based on the cited references. [See, for example, In re Fine, 5 USPQ2d 1596, 1958 (Fed. Cir. 1988) (wherein the Federal Circuit stated:

> The PTO has the burden under section 103 to establish a prima facie case of obviousness. . . . **It can satisfy that burden only by showing some objective teaching in the prior art** or that knowledge generally available to

> one of ordinary skill in the art that would lead the individual to combine the relevant references.

[Emphasis in bold added.] The Federal Circuit refers to **"the tempting but forbidden zone of hindsight"** in Loctite Corp. v. Ultraseal Ltd., 228 USPQ 90 at 98 (Fed. Cir. 1985).

Section 103 specifies that the obviousness of an invention is to be determined as of "the time the invention was made." Thus, prior art for purposes of applying Section 103 includes only references with effective dates before the priority date of the invention. The only other **prior art** reference cited in the 35 USC 103 rejections, based on the Oosterwijk et al. (a) and (b) references, is Raychaudhuri et al. which teaches nothing about the nature of the MN protein to overcome the teachings away from the MN protein of the Oosterwijk et al. (a) and (b) references.

Since the procedures used in the Oosterwijk et al. (a) and (b) references especially in view of the "unspecific material" used as the immunogen ["a cell homogenate from primary RCC lesions obtained from different patients" (Oosterwijk et al., WO 02/062972, page 2, lines 9-11)] could not necessarily produce MN-specific antibodies, but instead would produce a great spectrum of many antibodies, to probably thousands or more non-MN proteins, Applicants respectfully conclude based on the

patent case law, including Federal Circuit cases, such as, In re Robertson, supra, that a prima facie case of obviousness has not been established by the 103(a) rejections of the Final Office Action as maintained in the Advisory Action. Further details concerning the reasons why the said 103(a) rejections cannot establish prima facie obviousness are set forth below, as found in the response to the April 11, 2005 response to the Final Office Action.

Response to 103(a) Rejections Based upon Oosterwijk et al. (a) and (b) References as Set Forth in the April 11, 2005 Response to the Final Office Action

In accordance with the instructions provided by the Examiners in the telephone interview of March 7, 2005, Applicants are submitting evidence herewith that the hybridoma that secretes the G250 Mab ("G250 hybridoma") had not been deposited at an international depository under the Budapest Treaty, nor had the G250 Mab, the G250 protein or the G250 nucleic acid been characterized or identified at the earliest U.S. priority date claimed for the instant application, that is, October 21, 1992.

Claims 22, 30, 36-38, 42-43, 46-48 stand "rejected under 35 U.S.C. 103(a) as being unpatentable over Oosterwijk et

al [a] (WO 88/08854) as evidenced by Uemura et al [Br. J. Cancer, 81(4): 741-746, 1999] and as evidenced by Pastorek et al [Oncogene, 9: 2877-2888, 1994] in view of Raychaudhuri et al. [J. Immunology 139(1):271-278, 1987]. . . ." [Office Action, page 13, Section 12.] The Office Action continues at pages 14-15:

> [I]f the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. . . . **[I]t is Mab G250 taught by Oosterwijk et al [a] that is the relevant antigen for the production of an anti-idiotypic antibody**. . . . Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have produced an anti-idiotype antibody to Mab G250 as a therapeutic composition for treating renal cell carcinomas.

[Final Office Action, Section 12, pages 14-15; emphasis added.]

The above quoted statements presuppose that one of skill in the art has in his or her possession the G250 Mab, a method of producing the G250 Mab **or any MN-specific antibody** [phrase in bold added to April 11, 2005 response] reproducibly, the G250 antigen and/or the G250 cDNA. As pointed out above in describing the March 7 telephone interview, and in the arguments and facts made of record herein and in the earlier prosecution of the instant application, none of the prior art references, alone or in any combination, and certainly not Oosterwijk et

al., WO 88/08854 as will be shown in detail below by Oosterwijk et al.'s own admissions, provides sufficient information for one of skill in the art to produce reproducibly the **G250 Mab or any MN-specific antibody**. [Emphasis added to April 11, 2005 response.]

As discussed at page 48 of Applicants' response to the first Office Action and as confirmed by Oosterwijk et al. (see below), the G250 hybridoma cell line was not deposited until 2001 and therefore, at the time of filing the instant invention one of skill in the art would not have been able to produce the G250 Mab reproducibly [**or for that matter any MN-specific antibody** (phrase in bold added to April 11, 2005 response)], let alone anti-idiotype antibodies to antibodies that specifically bind the MN protein. Moreover, the company, who has been working with Oosterwijk et al. on the G250 Mab, Wilex AG, dropped an opposition to Zavada et al.'s European MN patent [EP-B 0 637 336] (corresponding to the instant application's earliest U.S. priority application) in favor of taking a license under the Zavada et al. patents/applications, constituting further evidence that WO 88/08854 did not render obvious the claimed invention.

The deficiencies of Oosterwijk et al., WO 88/08854, cannot be filled by the other cited references of the instant

rejection (or for that matter by any prior art reference) in that the only other cited references that concern MN are Pastorek et al. (1994) and Uemura et al. (1999), neither of which are part of the prior art, having each been published years after the earliest U.S. priority date for the subject claims, that is, October 21, 1992. Raychaudhuri et al. (1987), although part of the prior art, was cited only to show what was conventionally known about preparing anti-idiotype antibodies at the time the claimed invention was made, and has no relation whatsoever with MN per se.

1. Oosterwijk et al. Admissions that WO 88/08854 Provided No "Informations" Concerning the G250 Mab Nor the G250 Hybridoma Other Than a General Immunization Protocol

Oosterwijk et al. filed a new G250 Mab-related application, WO 02/062972 [submitted as Appendix 3; filed February 7, 2002, with a priority date of February 7, 2001.] In Example 1 of WO 02/062972 [and of its corresponding U.S. application - U.S. 2004/0077081 A1 (published April 22, 2004)], Oosterwijk et al. admit that **WO 88/08854 provided very little information about the G250 Mab and G250 hybridoma**:

> The G250 hybridoma cell line was produced as described in Example 1 of WO88/08854. Therein a general immunization protocol is given. **Further informations** [sic], **e.g. a molecular characterization of the G250**

antibody and the G250 hybridoma cell are lacking.

[WO 02/062972, page 8, lines 18-21; emphasis added.]

Further, at page 2 of WO 02/062972, Oosterwijk et al. acknowledge:

> The production of a hybridoma cell line expressing G250 antibody was generally described in the international patent application WO88/08854 and Oosterwijk et al. (supra). As stated above, a cell homogenate from primary RCC lesions obtained from different patients and thus **an unspecific material was used as an immunogen**. Furthermore, **the hybridoma cell line had not been deposited with a recognized depository institution according to the Budapest Treaty.** Thus, **an exact reproduction of the G250 hybridoma cell line from the publically available prior art documents does not seem to be possible**.

[WO 02/062972, page 2, lines 6-15; emphasis added.]

As disclosed above by Oosterwijk et al., "**an unspecific material was used as an immunogen**" to produce the hybridoma cell line expressing G250 antibody described in international patent application WO88/08854, and "**an exact reproduction of the G250 hybridoma cell line from the publically available prior art documents does not seem to be possible**." Therefore, Oosterwijk et al. WO 88/08854 admits by those statements, and by their actions in filing a PCT application published as WO 02/062972 A2 [and as US 2004/0077081 A1] clearly

admit that one of skill in the art **could not have produced the G250 Mab or any other MN-specific antibody based on the Oosterwijk et al. WO 88/08854 disclosure.** [Emphasis added to April 11, 2005 response.]

2. The G250 Hybridoma Not Deposited until September 2001

As indicated above, Oosterwijk et al. admitted that the G250 hybridoma was not deposited with an international depository under the Budapest Treaty until September 11, 2001. The European Examiner of the Oosterwijk et al. 1988 European application indicated at page 3 of the first Communication that ". . . the monoclonal antibody producing hybridomas of the application are not deposited and thereby not reproducible. . . . In this respect, the application does not fulfill the requirement of Article 83 regarding the disclosure of microorganisms as set out in Rule 28 EPC."

Oosterwijk et al. specifically admit in the PCT application WO 02/062972 [and corresponding US 2004/0077081 A1] that the "first publically available disclosure" of the G250 hybridoma and Mab was made by its September 11, 2001 deposit of the G250 hybridoma.

> Thus, the present invention relates to a hybridoma cell capable of producing a G250 monoclonal antibody. **This hybridoma cell**

was deposited under the Budapest Treaty for the Deposit of Microorganisms on September 11, 2001 at Deutsche Sammlung von Mikroorganismen und Zellkulturen GmbH (DSMZ), Mascheroder Weg 1b, 38124 Braunshweig, Germany under the Accession Number DSM ACC 2526. **The deposit is the first publically available disclosure of a G250 antibody producing hybridoma cell line**.

[WO 02/062972, page 2, lines 25-32; US 2004/0077081 A1, page 1, ¶ 0008; emphasis added.]

3. Owner of the WO 88/08854 Patent Dropped Opposition to MN European Patent in Favor of License to Zavada et al. Patents/Applications

As further evidence of the non-obviousness of the claimed invention over Oosterwijk et al., alone or in combination with any other prior art reference, Applicants respectfully inform the Examiner that Wilex AG, the company listed as the Applicant on Oosterwijk et al. WO 02/062972 A2, filed an opposition to the Zavada et al. MN European patent EP-B 0 637 336, but after the instant Applicants rebutted Wilex's opposition arguments, Wilex dropped the opposition in favor of licensing rights to the relevant Zavada et al. patents/applications.

4. Combination of References: Oosterwijk et al., Uemura et al., Pastorek et al. and Raychaudhuri et al.

As indicated above, Applicants respectfully submit that the deficiencies of Oosterwijk et al. WO 88/08854 are not corrected by any combination of Uemura et al., Pastorek et al. and Raychaudhuri et al. for the above-stated reasons. Applicants respectfully conclude that Oosterwijk et al. does not enable the G250 Mab **nor any other MN-specific antibody**, [phrase in bold added to April 11, 2005 response] since neither the G250 Mab nor the G250 antigen is identified by any biochemical characteristics, but is only given a name in the cited reference WO 88/08854, and was not accompanied by a deposit of the G250 hybridoma. Without knowledge of how to reproducibly make the G250 Mab **or any other MN-specific antibody**, [phrase in bold added to April 11, 2005 response] Raychaudhuri et al. is insufficient to overcome the deficiencies of Oosterwijk et al.

The fact that years later the MN protein is shown to be identical with the G250 antigen, as reported in Uemura et al. (1999), tells one of skill in the art nothing at the time the claimed invention was made, when only insufficient and misleading information had been disclosed about the identity of the G250 antigen. Then Pastorek et al. (1994), another reference that is not part of the prior art, has no relevance as

any form of evidence, as there was no link between the G250 antigen and the MN protein that could have been made by one of skill in the art at the time the claimed invention was made, based on the prior art disclosures.

Applicants respectfully request that the Examiner reconsider the instant rejection in view of the above facts, evidence and analysis, and withdraw the second 103(a) rejection.

35 U.S.C. § 103(a) (Section 13 of the Office Action)

> Claims 22, 30, 36-38, 42-43, 46-48 stand
>
> rejected under 35 U.S.C. 103(a) as being unpatentable over Oosterwijk et al (International Journal of Cancer, 38:489-494, 1986, Ids 10/19/2001) as evidenced by Uemura et al [Br. J. Cancer, 81(4): 741-746 (1999)] and as evidenced by Pastorek et al [Oncogene, 9: 2877-2888 (1994)] in view of Raychaudhuri et al [J. Immunology, 139(1): 271-278 (1987)]. . . .
>
> The response argues as above and the rebuttal to these arguments is as above. . . ."

[Office Action, page 16, Section 13.] Applicants respectfully traverse that rejection, relying on arguments presented in the previous section [**as well as those made in response to earlier office actions** (phrase in bold added to April 11, 2005 response)], noting that most of the disclosure of the Oosterwijk et al. 1986 article (International Journal of Cancer) is

contained within the Oosterwijk et al. application (WO 88/08854). Applicants respectfully point out that Oosterwijk et al. 1986, the only reference not cited in the second 103(a) rejection above, does not contain any disclosure further than Oosterwijk et al. WO 88/08854, concerning how one of skill in the art **would produce reproducibly the G250 Mab or any other MN-specific antibody** [emphasis in bold added to April 11, 2005 response], or any information about how one would be able to identify the G250 protein or cDNA. Therefore, Oosterwijk et al. 1986 cannot cure the deficiencies of Oosterwijk et al. WO 88/08854, which was filed after Oosterwijk et al. 1986 was published.

There is nothing in Oosterwijk et al., alone or in combination with any other prior art reference, such as Raychaudhuri et al. (1987), that would enable "one of ordinary skill in the art . . . to make or synthesize" **a MN-specific antibody** [emphasis in bold added to April 11, 2005 response], let alone the claimed anti-idiotype antibodies, which comprise an internal image corresponding to a **naturally occurring** [words in bold added to April 11, 2005 response] MN protein/polypeptide epitope until after the disclosure provided in the earliest U.S. priority application for the instant application. Applicants respectfully rely on the facts, evidence and analysis provided

above to overcome the instant rejection wherein Oosterwijk et al. 1986 replaces Oosterwijk et al. WO 88/08854.

In specific reference to the cited Oosterwijk et al. 1986 Int. J. Cancer article, Oosterwijk et al. WO 02/062972 stated the following:

> The production of a hybridoma cell line expressing G250 antibody was generally described in the international patent application WO88/08854 and Oosterwijk et al. (supra) [**i.e., Oosterwijk et al., Int. J. Cancer 38:489-494, 1986**]. As stated above, a cell homogenate from primary RCC lesions obtained from different patients and thus an unspecific material was used as an immunogen. Furthermore, the hybridoma cell line had not been deposited with a recognized depository institution according to the Budapest Treaty. Thus, **an exact reproduction of the G250 hybridoma cell line from the publically available prior art documents does not seem to be possible**.

[WO 02/062972, page 2, lines 7-15; emphasis added.]

According to Oosterwijk et al., prior to the 2001 priority date for WO 02/062972 A2 (and the corresponding US 2004/0077081 A1) [well after the earliest U.S. priority date claimed for the instant invention], one of skill in the art would not have been able to reproducibly make the G250 antibody from the "publically available prior art documents". Those "publically available prior art documents" would then **include** the cited Oosterwijk et al. (1996), Uemura et al. (1999),

Pastorek et al. (1994) and Raychaudhuri et al. (1987) documents. That admission by Oosterwijk et al. is further evidence of the lack of enablement provided by the cited references, even the non-prior art references, for the production of the G250 Mab.

Since nothing in Raychaudhuri et al. (1987) corrects the deficiencies in Oosterwijk et al. (1986) for the reproducible production of the G250 Mab **or for any MN-specific antibody** [phrase in bold added to April 11, 2005 response], or identification of the G250 antigen, and since Uemura et al. (1999) and Pastorek et al. (1994) only provide evidence published after the priority date of the instant application that the G250 antigen is identical to the MN antigen, but do not correct the deficiencies of Oosterwijk et al. 1986 for the reproducible production of the G250 Mab **or any other MN-specific antibody** [phrase in bold added to April 11, 2005 response] or identification of the G250 antigen at the time the claimed invention was made, there is nothing in the cited combination of references that would suggest or render obvious the claimed invention.

One of skill in the art with the disclosure of Oosterwijk et al. 1986 and Raychaudhuri et al. (1987) at the time the claimed invention was made, could not have reproducibly made the G250 Mab **or any other MN-specific antibody** [phrase in

bold added to April 11, 2005 response] or the G250 antigen by Oosterwijk et al.'s own admissions, let alone the claimed anti-idiotypic antibodies comprising an internal image corresponding to **a naturally occurring** [words in bold added to the April 11, 2005 response] MN protein/polypeptide epitope.

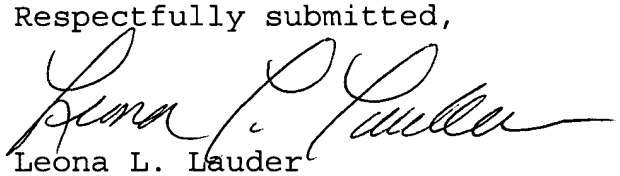
Applicants respectfully conclude neither Oosterwijk alone or as evidenced by Pastorek et al. 1994 and Uemura et al. 1999 in view of Raychaudhuri et al. renders the instantly claimed invention obvious, but instead as explained above is evidence of the nonobviousness of the instant invention. Applicants respectfully request that the Examiner reconsider the instant rejection in view of the above noted facts, evidence and analysis, and withdraw the subject third 103(a) rejection.

CONCLUSION

Applicants respectfully conclude that the claims are in condition for allowance, and earnestly request that the claims be promptly allowed. If for any reason the Examiner feels that a telephone conference would expedite the prosecution

of the subject application, the Examiner is invited to telephone the undersigned Attorney for Applicants at (415) 981-2034.

Respectfully submitted,



Leona L. Lauder
Attorney for Applicants
Registration No. 30,863

Dated: June 13, 2005